REMARKS

Claims 1, 19, 23, and 24 have been amended. Claims 1-24 are in the application. However, claims 3, 4, 7, and 9-18 remain withdrawn from consideration pursuant to an election of species requirement, and, therefore, should be added back into the application upon finding that the independent claims are allowable.

Attached hereto is a marked-up version of the changes made to the claims by the above amendments. In the attached marked-up version of the claim amendments, additions are underlined and deletions are bracketed.

Rejection Under 35 U.S.C. § 112

Claims 1, 2, 5, 6, 8, and 19-24 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. More specifically, the Examiner has stated that while each of claims 19 and 23 is drawn to a composition and "a composition must have at least two separate components."

Applicants agree with the Examiner. By reciting in the preamble that the invention is directed to a composition, Applicants are necessarily inferring that there is at least one other compound in the composition other than the required "compound having the formula (I)." Although Applicants' intent is clearly implied, Applicants have amended the claims by specifically requiring that the composition further comprises "a level of contaminants that is non-toxic when the composition is administered to a patient in a quantity sufficient to provide a neuroprotective effect." Support for this amendment may be found at page 6, lines 5-19, which discloses that the compositions of the invention may contain trace levels of contaminants, but "should not exhibit any unacceptable levels of toxicity at the dosages at which they are applied" to achieve "neuroprotection under hypoxic or ischaemic conditions." It is respectfully submitted that the amendments to claims 19 and 23 define at least one other component (*i.e.*, contaminants) in the composition and, thus, overcome the rejection of claims 19-24.

The Examiner has also stated that the expression "substantially pure" in claim 1 is indefinite. Applicants respectfully disagree because the specification (page 6, lines 5-11) defines "substantially pure" to mean that there are not any significant amounts of contaminants detectable using high performance liquid chromatography. It is further stated that "levels of contaminant should be less than 1%." In order to expedite prosecution of the application, claim 1 has been amended by requiring that the claimed substantially pure compound has "less than 1% contaminants." It is respectfully submitted that the amendment to claim 1 overcomes the rejection of claims 1, 2, 5, 6, and 8.

In view of the above amendments, it is believed that all of the pending claims meet the requirements of 35 U.S.C. § 112.

Prior Art Rejection

Claims 1, 2, 5, 6, 8, and 19-24 have been rejected under 35 U.S.C. § 103 as being unpatentable over Cherksey (U.S. 5,242,947). The Examiner has correctly noted that the Cherksey reference fails to teach or suggest the claimed compound having the required carbon atom "in the L configuration." The Examiner, however, has not provided any explanation as to how one having ordinary skill in the art might be motivated to modify the teachings of Cherksey `947 so that the required compounds are produced rather than a mixture of stereoisomers. On this basis alone, the claims are allowable over the prior art of record.

The Examiner has admitted that the Cherksey `947 patent does not teach substantially pure compounds as claimed. Further, the Examiner has not explained how one having ordinary skill in the art would be motivated to modify the teachings of Cherksey to provide substantially pure compounds as claimed. Cherksey does not disclose a method of making pure compounds as claimed. Evidence of this is in the attached Supplemental Declaration of Lars E. Sundstrom, which states that the methods disclosed in Cherksey WO 93/12777 (the identical methods disclosed in the `947 patent) do not yield substantially pure compounds. To the contrary, the methods disclosed by Cherksey produce an extremely impure composition comprising only about 1% or less of the desired compound. Not only does the Cherksey `947

patent fail to provide an enabling disclosure for a substantially pure compound as claimed, but Cherksey does not even recognize that his methods produce impure compositions containing less than 1% of the desired compound or that the low purity products are toxic and lack the desired utility.

The attached Declaration is evidence that the reaction conditions disclosed by Cherksey will inevitably lead to a mixture of different compounds, not the required pure compound. While the desired reaction involves activation of acid groups and selective reaction with one amine, there are, in fact, many more possibilities. More specifically, there are two amines and one acid group on one of the reactants, and the polyamine has three amine groups. Further, each amine group is different, therefore, the reaction product will not be pure and will not yield the desired compound in only the L isomer form.

Using the techniques of Cherksey, various reactions will occur, such as the central N attacking an arginine amine and condensing with itself. Also, there will be dimers from the three different amines on the polyamines and trimers. In fact, the major product of the Cherksey reaction will be hydrolyzed arginine esters.

Further, using a pH of 14, as disclosed by Cherksey, will lead to loss of stereochemical integrity, which will lead to further impurities.

If it were known that the crude products of Cherksey were impure and contained undesirable levels of toxic compounds, then one having ordinary skill in the art may logically wish to utilize purification techniques to produce the desired compounds. The products of Cherksey, however, could not be purified in the L isomer form from the mixture using standard purification techniques. Any skilled chemist would realize that the compounds in the mixture have the same formal charge and that ion-exchange techniques would not be useful for separating the isomers. Further, a person skilled in the art would not even attempt to purify such a mixture, as the person of ordinary skill in the art would not expect to succeed in obtaining a separation of the different compounds in the mixture, let alone the individual isomers. Nevertheless, the Cherksey patent does not disclose that the synthesis techniques identified therein would inevitably lead to undesirable mixtures or that purer compositions

would be desirable. Accordingly, those having ordinary skill in the art would not be motivated by the prior art to modify the teachings of Cherksey to achieve the required purity levels.

Further, a person of ordinary skill in the art would know that chromatographic techniques would not be suitable for separating the desired compounds, especially the stereoisomers.

The Examiner has criticized the Declaration of Lars E. Sundstrom filed January 23, 2002, on grounds that it does not state the exact starting compounds, the solvents used, the temperature of the reaction, and other conditions. This is incorrect. As set forth in the attached supplemental Declaration of Lars E. Sundstrom, the methods of Cherksey (WO 93/12777) were reproduced exactly. More specifically, L-arginine ethyl ester was dissolved in 5 ml of one N sodium hydroxide, and an equimolar amount of spermidine was added dropwise. The reaction was allowed to proceed at 25°C at a pH of 14 under stirring. The reaction was continued for a period of 12 hours. All of this information is disclosed in the WO 93/12777 document, and this was the exact procedure used by Applicants to evaluate the products in accordance with the teachings of Cherksey.

Thus, as previously stated, the Cherksey reference discloses all of the conditions which the Examiner has required. Applicants, therefore, have established that the Cherksey reference does not provide an enabling disclosure for the claimed substantially pure compounds and/or compositions.

The Examiner's speculation relating to what might be possible with respect to purification techniques and/or alternative synthesis techniques is not evidence of non-obviousness. More specifically, the Examiner's speculation as to purification techniques and synthesis techniques does not constitute prior art. Moreover, as stated above, the prior art does not provide any suggestion that purification or improved synthesis techniques are required. Further, the purification techniques suggested by the Examiner would not separate the stereoisomers and, therefore, would not meet the requirements of the claims.

For all of the reasons above, it is respectfully submitted that the rejection should be withdrawn in view of the amendments and attached Supplemental Declaration of Lars E. Sundstrom.

Claims 1, 2, 5, 6, 8, and 19-24 have been rejected under 35 U.S.C. § 103 as being unpatentable over Cherksey (`947) in view of Bodansky (*Int J Pept Prot Res 25, 449-474 1985*). Bodansky discloses the use of protecting groups during peptide synthesis. Briefly, the Examiner has supposed that the ordinary chemist would "recognize an optimal yield would be obtained if there were just one electrophile (the carboxyl group or active ester thereof) and one nucleophile (the amine reactant)" for the arginine used in the synthesis described by Cherksey. The Examiner further speculates as to what one having ordinary skill in the art might do if they had some way of knowing it would be desirable to obtain Applicants' claimed substantially pure compounds and compositions.

The Examiner's argument is clearly flawed. It supposes that those having ordinary skill in the art would have understood that the teachings of Cherksey do not provide useful compounds or compositions and that useful compounds and compositions could be obtained utilizing alternative synthesis techniques which are capable of producing Applicants' claimed compounds and compositions. It is not, however, the prior art that teaches the desirability of the claimed substantially pure compounds, that Cherksey's techniques do not provide satisfactory results, or why Cherksey's techniques do not provide satisfactory results. It is only through the guidance provided by Applicants' disclosure that one having ordinary skill in the art would understand how the teachings of Cherksey could be modified to achieve improved results. It is not enough that the prior art teaches the possibility of the invention, it must provide some suggestion or motivation for the claimed invention.

The teachings of Bodansky were available to Cherksey at the time the Cherksey application was filed. Accordingly, Cherksey could have used the methods taught by Bodansky. Cherksey, however, apparently did not find it obvious to utilize the methods of Bodansky. Regardless, the prior art does not teach the desirability of the claimed substantially pure compounds and compositions, or the desirability of producing the substantially pure L-isomer.

A person having ordinary skill in the art would not be motivated to combine the teachings of Cherksey with Bodansky because there is not any teaching that the L-isomer is the active isomer. In fact, a person having ordinary skill in the art, when faced with the disclosure of Cherksey and the discovery that the products are lethal, would decide not to use the compounds at all.

For all of the reasons set forth above, it is respectfully submitted that the prior art does not teach, suggest, or provide motivation for the claimed invention, and it is only by combining the prior art with Applicants' own teachings that one having ordinary skill in the art would understand the relevance of combining the teachings of Cherksey with Bodansky. Accordingly, withdrawal of the rejection is most appropriate.

The Examiner has restated the rejection of claims 1, 2, 5, 6, 8, and 19-24 under 35 U.S.C. § 103 based on the Cherksey `947 patent but has provided slightly different rational. This does not constitute a separate rejection. Further, the various arguments and issues set forth (lines 5+ at page 8 and lines 1-3 at page 9) have been addressed above. Accordingly, the rejection is improper and should be withdrawn for the reasons generally set forth above with respect to the same rejection using a slightly different rationale. More specifically, regardless of whether it would have been obvious to utilize high performance liquid chromatography to separate the components from the products of Cherksey, such utilization of high performance liquid chromatography would not result in separation of the stereoisomers and would not provide the claimed products. Therefore, withdrawal of the rejection in view of the above amendments, the attached Supplemental Declaration, and above remarks is appropriate and earnestly solicited.

Claims 1, 2, 5, 6, 8, and 19-24 have been rejected under 35 U.S.C. § 103 as being unpatentable over Cherksey in view of the Aldrich Catalog, 1992-1993 edition. The Aldrich Catalog discloses both the L-arginine and D-arginine isomers. The Examiner has alleged that one having ordinary skill in the art would have been motivated to use the L-arginine isomer in the synthesis of the claimed compounds because the L-isomers are less expensive and L-isomers generally exhibit greater biological activity.

Applicants' do not stipulate to the Examiner's allegation that those having ordinary skill in the art would always or usually expect an L-isomer to exhibit greater biological activity. As stated above, the conditions employed by Cherksey, especially the very high pH (14), would lead to a loss of stereochemical integrity and would result in products having a mixture of stereoisomers, regardless of whether an L-isomer reactant, a D-isomer reactant, or a combination of both are used during the synthesis process disclosed by Cherksey.

Moreover, the reactants disclosed by the Cherksey reference are L-arginine ethyl ester and spermidine, not L-arginine. Thus, the price and/or biological activity of arginine are not relevant to the claimed invention since the use of L-arginine in the synthesis process taught by Cherksey would not lead to the substantially pure compounds of the claimed invention. Accordingly, withdrawal of the rejection is most appropriate.

Claims 1, 2, 5, 6, 8, and 19-24 have been rejected under 35 U.S.C. § 103 as being unpatentable over Cherksey `947 in view of Eldefrawi (*Proc. Natl. Acad Sci. U. S. A.* 85 (13) 4910-13, 1988). The Examiner has admitted that the Eldefrawi reference "does not disclose any of the claimed compounds." According to the Examiner, however, "Eldefrawi discloses reaction of a polyamine with an active ester of a protected amino acid, wherein all but one of the amino groups of the polyamine is protected." The Examiner has also speculated on a synthesis scheme which one having ordinary skill in the art might propose based on a combination of Cherksey in view of Eldefrawi.

Rather than provide a formal basis for rejection which meets the requirements of 35 U.S.C. § 103, the Examiner has instead concluded that the rejection is proper because "If a synthetic organic chemist of ordinary skill were presented with the 'target' compound (Cherksey), together with a suggestion to use the procedures disclosed in Eldefrawi, he would have had no difficulty obtaining the target compound."

The flaw in the Examiner's conclusion is readily apparent on its face. The "target" substantially pure compounds of the claimed invention are not taught or suggested by the prior art. Thus, because the "synthetic organic chemist of ordinary skill" was not "presented with the 'target' compound" but was instead presented with a different (unpure) compound alleged to

provide utility, the ordinary artisan would not find the claimed substantially pure compounds obvious. Whether one having ordinary skill in the art would have had any difficulty making the claimed compounds is not relevant to patentability under 35 U.S.C. § 103. To the contrary, if one having ordinary skill in the art would have difficulty making the claimed compounds, then there may be some question as to whether or not there is enablement for the claimed compounds. Regardless, the combination of Cherksey in view of Eldefrawi does not provide motivation for the claimed substantially pure compounds having the required chirality.

For the reasons set forth above, it is respectfully submitted that withdrawal of the rejection based on Cherksey in view of Eldefrawi is appropriate.

Claims 1, 2, 5, 6, 8, and 19-24 have been rejected under 35 U.S.C. § 103 as being unpatentable over Cherksey `947 in view of Hashimoto (*Tetrahedron Lett.* 28 (30) 3511-14, 1987).

The Examiner has admitted that "Hashimoto does not disclose any of the claimed compounds." Rather than provide a formal rational meeting the requirements of 35 U.S.C. § 103, the Examiner has merely concluded that even if Cherksey is non-enabling with respect to the claimed substantially pure compounds, "it is not true for Cherksey taken in view of Hashimoto."

It is respectfully submitted that this rejection is fatally flawed because it does not explain how one having ordinary skill in the art would be motivated to modify the teachings of Cherksey by selectively employing the teachings of Hashimoto.

Further, the synthesis method disclosed by Cherksey in view of Hashimoto would not assist a skilled person to prepare the required L-isomer of the claimed substantially pure compound. The modifications required to the synthesis would not be apparent to a person of ordinary skill in the art. Accordingly, withdrawal of the rejection based on Cherksey in view of Hashimoto is most appropriate.

CONCLUSION

Applicants have enclosed evidence (attached Supplemental Declaration under Rule 1.132) showing that the Cherksey reference does not provide enablement for the claimed substantially

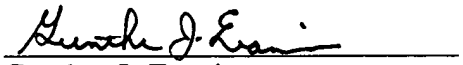
pure compounds. Further, none of the prior art references provide any teaching, suggestion, or motivation for providing substantially pure compounds as claimed, and none of the prior art references provide motivation for modifying the teachings of Cherksey to achieve the required substantially pure L-isomer. Accordingly, withdrawal of all prior art rejections and allowance of the claims is requested.

Respectfully submitted,

LARS E. SUNDSTROM ET AL.

By: Price, Heneveld, Cooper,
DeWitt & Litton

April 16, 2003
Date



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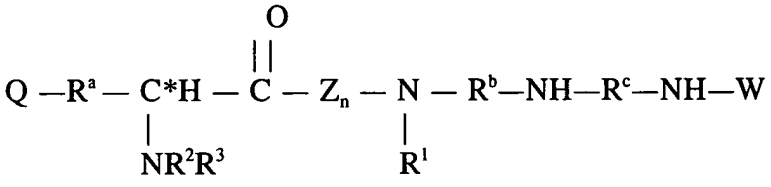
APPENDIX A
Version With Markings to Show Changes Made

1. (Thrice Amended) A substantially pure compound <u>having less than 1% contaminants and</u> having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group, or hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

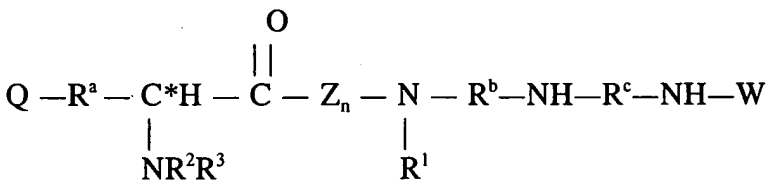
R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof.

19. (Twice Amended) A composition consisting essentially of a compound having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group, or hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

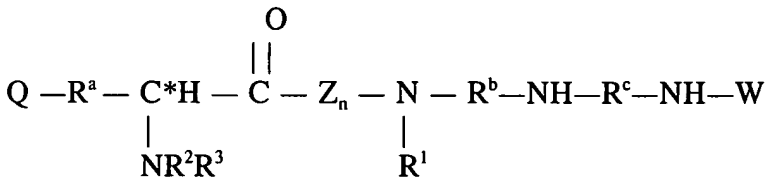
W represents a hydrogen atom or an alkyl or aryl group; and

substituents α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof;

the composition further comprising a level of contaminants that is non-toxic when the composition is administered to a patient in a quantity sufficient to provide a neuroprotective effect.

23. (Twice Amended) A non-toxic composition consisting essentially of a compound having the formula (I)



(I)

wherein:

Q represents an amidino group, a cyano group or a group of formula XYN-, where

X and Y are the same or different, and each may represent a hydrogen atom, a lower alkyl group, or hetero-atom containing group or, together with the nitrogen atom to which they are attached, form a nitrogen-containing heterocyclic group;

R^a represents a straight or branched chain alkylene or alkenylene group having from 1 to 6 carbon atoms and each optionally being substituted by from 1 to 4 alkyl groups each having from 1 to 3 carbon atoms;

R^b and R^c represents an alkylene or alkylene group having 3 or 4 carbon atoms in a straight chain, each being optionally substituted by a 1 or 2 alkyl groups each having from 1 to 3 carbon atoms, the total number of carbon atoms in said straight chains of R^b and R^c being 7;

R^2 and R^3 are the same as or different from each other and each represents a hydrogen atom, or a group of formula R, RCO-, ROCO-, or RNHCO-, where

R represents a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

the chiral carbon atom indicated by the asterisk is in the L configuration;

Z is an aromatic amino acid residue;

n is 0 or 1;

R^1 represents a hydrogen atom or a lower alkyl group or an aryl group, said alkyl or aryl group being optionally substituted by one or more of the substituents α, defined below;

W represents a hydrogen atom or an alkyl or aryl group; and

substituents α are selected from: halogen atoms, amino groups, alkylamino groups, dialkylamino groups, cyano groups, hydroxy groups, alkyl groups (except when the substituted group is akyl), aryl groups, carbamoyl groups, alkylcarbamoyl groups, dialkylcarbamoyl groups and carboxy groups and esters thereof;

and pharmaceutically acceptable salts thereof;

the composition further comprising a level of contaminants that is non-toxic when the composition is administered to a patient in a quantity sufficient to provide a neuroprotective effect.

24. (Twice Amended) The composition of claim 23 which contains less than [~~1%~~] 0.1% of contaminants.

IN THE UNITED STATES PATENT OFFICE

APPLICATION OF)
)
LARS E. SUNDSTROM)
)
SERIAL NUMBER 09/581,397)
)
FILED: October 2, 2001)
)
TITLE: NEUROPROTECTIVE AGENTS)

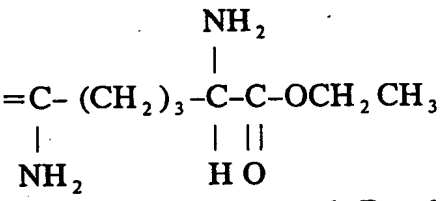
SUPPLEMENTAL DECLARATION UNDER RULE 1.132

I, Lars E. Sundstrom, hereby declare the following:

A foundation for my statements is set forth in my Declaration of October 24, 2001, relating to the above-referenced application, the entire contents of which are reaffirmed and incorporated herein. A copy of my Declaration of October 24, 2001 is attached hereto.

In my October 24, 2001 Declaration, I stated that "the methods described in WO 93/12777 were reproduced exactly in an attempt to synthesize arginine-spermidine and lysine-spermidin." The conditions used during the synthesis process are disclosed at page 29, lines 26-36 of the WO 93/12777 document. These conditions are quoted directly from the document as follows:

p. 29, l 26:

L-arginine ethyl ester 

also from Sigma was used to synthesize compounds B and A, above. Briefly, the synthesis of Compound B involved use of $3X10^{-3}$ moles of L-arginine ethyl ester which was dissolved in 5ml of 1N NaOH. An equimolar amount of spermidine was added dropwise and the reaction was allowed to proceed at 25`[°]C, pH 14 under stirring. The product was brought to pH 7.4 by addition of 5N HCl. The reaction was continued for 12 hours.

The compounds prepared in accordance with the teachings of WO 93/12777 were impure (at least 99% impure), toxic and without therapeutic effect.

The applied prior art Cherksey references do not disclose that the compounds prepared in accordance with the teachings therein are in impure form, toxic or non-therapeutic.

European Patent Application No. 98960031.7, corresponding to the above-referenced U.S. Application (09/581,397), has been accepted for grant with claims directed to substantially pure compounds. During prosecution of the corresponding European application, the Cherksey references were considered not to provide an enabling disclosure of the pure compound, in the L-isomer form.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true, and further, these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

02 03 03
Date

Lars E. Sundstrom